1. SUMMARY

The report describes in vitro skin permeation characteristics of transdermal delivery systems (TDS) containing SPM8224, the free base of Fesoterodine. Test samples were prepared by either lab-scale solvent coating or hot-melt processing. Patches were tested by means of flux rates across hairless mouse skin, selected samples were also investigated in the LACDR human skin model.

High flux rates of SPM8224 across mouse skin were obtained for all batches. The highest initial flux was achieved with a silicone based hot melt formulation.

Permeation across human skin demonstrated the promising potential of SPM8224, the free base of Fesoterodine, for the treatment of overactive bladder. Based on these in vitro data patches with sizes in the range of 15 to 30 cm² could theoretically delivery 4 to 8 mg/24 h which is the current range of the oral Fesoterodine formulation. The data have to be confirmed in vivo.

Besides this, new acrylic based hot melt adhesive from National Starch & Chemical were evaluated. One very promising formulation could be identified. Provided that other success criteria, such as physico-chemical compatibility with the hot melt process and with different drugs, are met these formulations might fill the gap in hot melt pressure sensitive adhesives for transdermal systems.

CONTENTS

2. INTRODUCTION AND OBJECTIVES

The objective of the study was to investigate the feasibility of transdermal delivery of SPM8224, the free base of Fesoterodine (scheme 1).
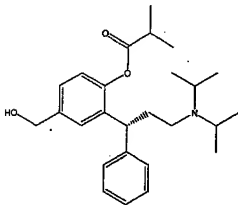
Scheme 1: Chemical structure of the free base of Fesoterodine

Therefore, several lab scale patch batches containing SPM8224 were prepared and invistigated by means of in vitro drug permeation across hairless mouse skin. Subsequently, selected samples were investigated in a human skin model, as well.

3. MATERIALS AND METHODS

For a detailed description of the experiments refer to the batch documentation.

Hot-melt patches (exemplary): 8 g of a preformed silicone adhesive were weighed into a beaker and tempered at 160°C for ca. 20 min to achieve a homogenous melt. 0.5 g of inner phase polymer (e.g. poly(ethylene oxide) and 1.5 g of drug were added. After tempering at 160°C for additional 5 min the mixture was homogenized manually and further processed on the pre-tempered Chill-Roll (120°C, 250 µm) for lamination.

5 cm² patches were isolated by manual punching followed by determination of the average patch weight (n=10). Finally, patches were sealed individually in pouches.

Mouse Skin Model (PHA): according to OBU0469.ABV100, rev. 00 (1998) with an active diffusion area of 2.55 cm², a phospate buffer acceptor phase at pH 6.2 and a temperature of 32°C, n=3

Human Skin Model (LACDR):
according to H. Tanojo et al. , J. Control Rel. 45 (1997) 41-47.
skin from abdomen with a thickness of approx. 250 µm, flux experiment: acceptor phase: PBS, pH= 6.2, temperature: 32°C, diffusion cells with spiral groove (8 cells), groove area: 0.552 cm², dialysis membrane used as separator between skin and acceptor phase
flux: 5 ml/hour PBS, experiment runs for 72 hours, sampling cycle: 3 hours

Analytical Methods (PHA): refer to certificates of analysis

Data Analysis: sigmoidal Boltzmann and linear fit: Microcal Origin 6.0

4. RESULTS AND DISCUSSION

The free base of Fesoterodine is an oily substance and was used with a purity of approx. 90%. Several lab scale patch batches with different compositions were prepared by either solvent coating or hot melt processing and the preparation presented no difficulties. The properties of these batches are summarized in table 1.

Table 1:   Properties of the patch batches

No	Lot No. (Ch.B.)	PSA	Theo. drug loading [% (w/w)]	Patch weight (n=10) [g/m²]
1	20111080	SC acrylic	15	100
2	20111085	HM EVA	15	84
3	20111086	HM silicone	15	63
4	20111087	HM SxS	15	89
5	20111095	HM acrylic 01	15	73
6	20201027	HM acrylic 02	15	121
7	20201028	HM acrylic 03	15	115

SC Acrylic   = solvent coating , acrylic type adhesive, Duro Tak 387-2287, National Starch & Chemical (NSC)
HM EVA   = hot melt, ethylene vinyl acetate co-polymer adhesive, Dispofix 213, NSC
HM Silicone   = hot melt silicone based adhesive, BioPSA + 5% (w/w) Ozokerite wax, DowCorning
HM SxS   = hot melt, styrene block co-polymer, in house formulation
HM Acrylic 0x = hot melt acrylic type adhesives, experimental formulations from NSC, refer to Annex

All batches were tested in the hairless mouse skin model.

Fig. 1 outlines the cumulative permeation of SPM8224 across hairless mouse skin (HMS) from patches prepared with the most common adhesive classes, acrylic based, ethylene vinyl acetate based (EVA), silicone based and poly(styrene) based (SxS). The flux rates were expressed as permeation of active metabolite, which is the hydrolysis di-hydroxy product (SPM7605).
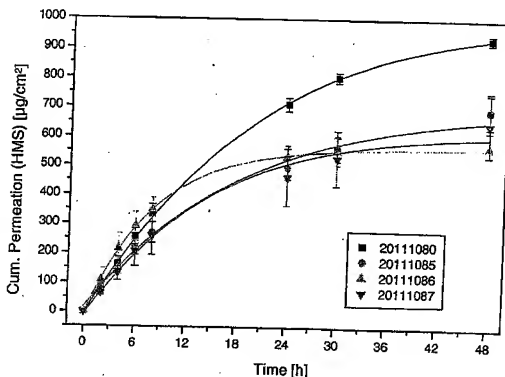
Fig. 1: Cumulative drug permeation (calculated as permeation of active metabolite, SPM7605)

In all cases high flux rates were observed following a non-linear release kinetics. The flux rates from EVA and SxS matrices were nearly identical. Higher initial rates were obtained for the silicone and the acrylic based systems. While the silicone type batch showed the highest drug permeation in the first 6 to 8 h, the subsequent higher values for the acrylic based patch were mainly due to a higher patch weight.

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Fig. 2 illustrates the drug permeation across hairless mouse skin (HMS) from new types of pressure sensitive adhesives (PSA): for the first time it was possible to test the performance of acrylic based patch batches which were prepared by hot melt processing. The three different experimental PSA were exclusively obtained from National Starch & Chemical.
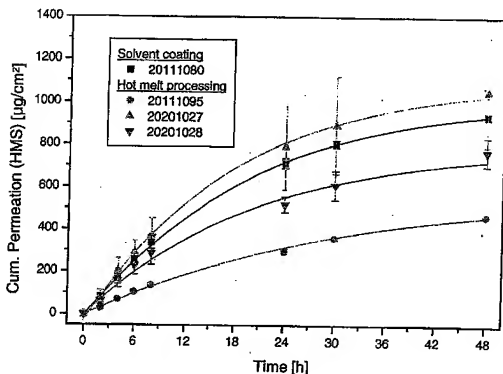
Fig. 2:   Cumulative drug permeation (calculated as permeation of active metabolite, SPM7605)

While two of these new PSA (batches 20111095 and 20201028) yielded lower flux rates, it was possible with the third PSA (batch 20201027) to achieve flux rates comparable to the solvent born system (batch 20111080). Although still in an experimental stage this new class of acrylic based PSA seems to be capable of closing the final gap in hot melt processing, since up to now the use of acrylics was limited to solvent coating, only.

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Two batches were investigated in the LACDR human skin model. Since the skin supporting silicone membrane in this model was hindering drug flux it was exchanged with a dialysis membrane. Fig. 3 demonstrates the obtained flux rates across the composite of excised human skin supported with a dialysis membrane (EHS/DM).
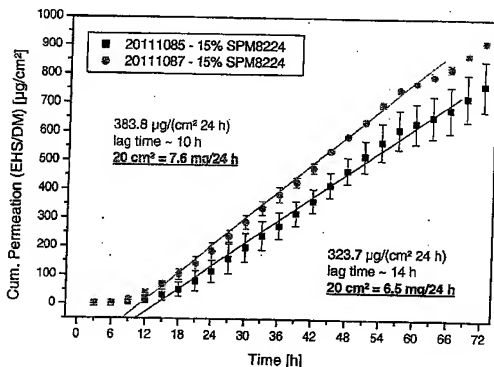
Fig. 3: Cumulative drug permeation (calculated as permeation of active metabolite, SPM7605)

After short lag-times of 6 to 8 h (which are not predictive for the in vivo situation) both batches showed a high steady state flux for at least 2.5 d. From these results patches with a size of already 20 cm² could theoretically deliver therapeutic doses of the free base of Fesoterodine, compared to the oral formulation.

CONCLUSIONS

Several lab scale patch batches containing the free base of Fesoterodine were prepared and tested by means of in vitro drug permeation across mouse skin and human skin.

Based on the results obtained, the flux rates were found to be sufficient for the treatment of overactive bladder with patch sizes in the range of 15 to 30 cm² (equal to ca. 4 to 8 mg/24 h).

Moreover, in cooperation with National Starch & Chemical a new series of hot melt acrylics could be developed. These new adhesives could close an actual gap in hot melt pressure sensitive adhesive (PSA) formulation for transdermal systems. To further evaluate this class of PSA an investigation on physico-chemical compatibility with the hot melt process and different drug substances has to be performed.

ANNEX 1

Copies of the Certificates of Analysis
(signed originals stored at PH DOK)

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	SPM 907	Ch.-B.:	20111080
Wirkstoff :	**SPM 8224**		
Sollgehalt :	15 %	TDS - Fläche:	5 cm²
ABV vom :	analog OB 0469.ABV.100	Analysendatum :	

Ausgangsanalyse

Bemerkungen:
Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
Mäusehautdicke: 1=161 µm; 2=168µm, 3=172µm, 34,5g
Alter lebend: 8 Wochen, TK-Schrank 10 Wochen SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	55,67	84,70	72,02	70,80	14,6
4	122,20	170,16	138,78	143,71	24,4
6	198,00	256,39	218,78	224,39	29,6
8	263,98	330,41	286,25	293,55	33,8
24	501,55	599,45	570,07	557,02	50,2
30	572,00	664,50	646,75	627,75	49,1
48	653,61	738,79	750,20	714,20	52,8

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=	74,6	µg
Regressionskoeffizient (m) =	20,83	µg/h
Korrelationskoeffizient (r) =	0,9786	3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	21,74	23,83	19,57	21,71	2,1
4	44,25	48,65	42,13	45,01	3,3
6	69,47	73,58	67,88	70,31	2,9
8	91,83	96,11	88,95	92,30	3,6
24	277,04	239,90	228,10	248,35	25,5
30	312,79	269,83	261,67	281,43	27,5
48	377,09	322,27	327,26	342,21	30,3

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=	6,0	µg
Regressionskoeffizient (m) =	10,17	µg/h
Korrelationskoeffizient (r) =	0,9990	3-24h

Datum	Fabert (PHA)	Dr. Seiffert(PHA)

SCHWARZ BIOSCIENCES

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	SPM 907	Ch.-B.:	20111085
Wirkstoff :	**SPM 8224**		
Sollgehalt :	15 %	TDS - Fläche:	5 cm²
ABV vom :	analog OB 0469.ABV.100	Analysendatum :	

Ausgangsanalyse

Bemerkungen:
Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
Mäusehautdicke:1=174 µm; 2=159µm, 3=190µm, 35,5g
Alter lebend: 8 Wochen, TK-Schrank 10 Wochen SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	58,74	72,97	104,26	78,66	23,3
4	121,08	130,31	162,74	138,04	21,9
6	188,37	183,76	239,35	203,82	30,8
8	238,21	223,26	286,98	249,48	33,3
24	410,84	379,08	463,27	417,73	42,5
30	470,84	428,55	518,49	472,63	45,0
48	572,15	507,03	629,89	569,69	61,5

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=	92,7	µg
Regressionskoeffizient (m) =	14,19	µg/h
Korrelationskoeffizient (r) =	0,9641	3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	14,65	18,20	20,52	17,79	3,0
4	32,93	34,65	34,64	34,07	1,0
6	52,29	50,29	53,65	52,07	1,7
8	67,36	52,25	66,03	61,88	8,4
24	163,98	136,16	146,39	148,84	14,1
30	187,17	156,71	164,01	169,30	15,9
48	246,26	207,59	207,87	220,57	22,2

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=	12,1	µg
Regressionskoeffizient (m) =	5,77	µg/h
Korrelationskoeffizient (r) =	0,9961	3-24h

Datum	Fabert (PHA)	Dr. Seiffert (PHA)

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	SPM 907 TDS	Ch.-B.:	20111086
Wirkstoff :	SPM 8224		
Sollgehalt :	15%	TDS - Fläche :	5 cm²
ABV vom :	analog OB 0469.ABV.100	Analysendatum :	

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT   Freisetzungsfläche 2,55 cm²
Mäusehautdicke:1=188 µm; 2=172µm, 3=167µm, 32,7g
Alter lebend: 9 Wochen, TK-Schrank 7 Wochen SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	151,6	86,7	72,8	103,7	42,0
4	264,1	194,6	165,7	208,1	50,6
6	329,6	274,1	234,0	279,2	48,0
8	370,9	340,3	291,7	334,3	39,9
24	438,3	538,7	479,3	485,5	50,5
30	442,8	556,4	503,5	500,9	56,8
48	444,3	563,8	521,3	509,8	60,6

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=   150,3   µg
Regressionskoeffizient (m) =   14,98   µg/h
Korrelationskoeffizient (r) =   0,9227   3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	28,0	18,2	18,3	21,5	5,6
4	52,4	37,3	38,3	42,7	8,5
6	69,4	51,7	53,3	58,1	9,8
8	82,4	64,3	66,5	71,1	9,8
24	127,3	122,2	138,2	129,2	8,1
30	131,6	130,6	149,8	137,3	10,8
48	135,5	138,8	162,2	145,5	14,6

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=   24,8   µg
Regressionskoeffizient (m) =   4,51   µg/h
Korrelationskoeffizient (r) =   0,9763   3-24h

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Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	SPM 907	Ch.-B.:	20111087
Wirkstoff :	**SPM 8224**		
Sollgehalt :	15 %	TDS - Fläche:	5 cm²
ABV vom :	analog OB 0469.ABV.100	Analysendatum :	

Ausgangsanalyse

Bemerkungen:
Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
Mäusehautdicke:1=170 µm; 2=162µm, 3=160µm, 31,3g
Alter lebend: 8 Wochen, TK-Schrank 10 Wochen SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1·cm²

Zeit [h]	1	2	3	MW	SD
2	44,72	59,11	64,84	**56,22**	10,4
4	85,65	140,79	132,93	**119,79**	29,8
6	121,63	218,35	205,37	**181,78**	52,5
8	150,10	269,83	254,75	**224,89**	65,2
24	257,35	417,04	435,07	**369,82**	97,8
30	317,34	466,51	490,29	**424,71**	93,7
48	384,12	541,07	603,89	**509,69**	113,2

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=	77,2	µg
Regressionskoeffizient (m) =	12,87	µg/h
Korrelationskoeffizient (r) =	0,9521	3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	17,57	20,90	16,42	**18,30**	2,3
4	33,57	45,48	32,25	**37,10**	7,3
6	49,28	70,25	50,44	**56,66**	11,8
8	62,80	89,55	64,09	**72,15**	15,1
24	137,51	190,84	138,64	**155,66**	30,5
30	157,04	214,82	156,88	**176,25**	33,4
48	204,06	268,98	203,75	**225,60**	37,6

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=	15,3	µg
Regressionskoeffizient (m) =	5,98	µg/h
Korrelationskoeffizient (r) =	0,9908	3-24h

Datum	Fabert (PHA)	Dr.Seiffert (PHA)

SCHWARZ BIOSCIENCES

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat : SPM 907 TDS   Ch.-B.:   20111095
Wirkstoff : SPM 8224
Sollgehalt : 15%   TDS - Fläche: 5 cm²
ABV vom : analog OB 0469.ABV.100   Analysendatum :
Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT   Freisetzungsfläche 2,55 cm²
Mäusehautdicke:1=182 µm; 2=169 µm, 3=176 µm,32,9 g
Alter lebend: 9 Wochen,   TK-Schrank 7 Wochen   SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	25,7	18,1	21,6	21,8	3,8
4	59,7	47,3	51,8	52,9	6,3
6	87,4	69,2	77,4	78,0	9,1
8	110,2	94,2	100,3	101,6	8,1
24	199,6	212,8	211,4	207,9	7,3
30	253,2	245,3	245,5	248,0	4,5
48	322,0	313,3	318,8	318,1	4,4

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b) =   22,4   µg
Regressionskoeffizient (m) =   7,96   µg/h
Korrelationskoeffizient (r) =   0,9849   3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	11,9	10,9	10,7	11,2	0,6
4	26,9	26,7	24,3	26,0	1,4
6	40,0	38,9	35,6	38,2	2,3
8	51,3	52,1	45,7	49,7	3,5
24	112,7	131,2	121,5	121,8	9,3
30	151,7	155,3	140,9	149,3	7,5
48	198,4	210,1	189,2	199,2	10,5

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=   6,5   µg
Regressionskoeffizient (m) =   4,87   µg/h
Korrelationskoeffizient (r) =   0,9965   3-24h

SCHWARZ // BIOSCIENCES

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	SPM 907 TDS	Ch.-B.:	20201027
Wirkstoff :	SPM 8224		
Sollgehalt :	15%	TDS - Fläche :	5 cm²
ABV vom :	analog OB 0469.ABV.100	Analysendatum :	

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT   Freisetzungsfläche 2,55 cm²
Mäusehautdicke:1=150 µm; 2=148 µm, 3=158 µm, 29,4g
Alter lebend: 8 Wochen, TK-Schrank 12 Wochen SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	51,3	109,4	80,4	80,4	29,0
4	129,0	217,5	232,3	192,9	55,9
6	208,8	300,8	308,0	272,5	55,3
8	261,7	364,5	422,5	349,6	81,5
24	549,2	591,4	966,0	702,2	229,4
30	634,2	633,6	1081,0	782,9	258,1
48	801,5	680,0	1236,8	906,1.	.292,8

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=	87,0	µg
Regressionskoeffizient (m) =	26,42	µg/h
Korrelationskoeffizient (r) =	0,9836	3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	14,1	20,5	17,3	17,3	3,2
4	32,2	41,9	56,9	43,7	12,5
6	49,3	59,5	73,1	60,6	12,0
8	65,2	77,4	93,1	78,6	14,0
24	180,8	217,9	213,9	204,2	20,3
30	216,1	248,6	256,0	240,2	21,2
48	284,6	290,7	313,5	296,3	15,2

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=	8,4	µg
Regressionskoeffizient (m) =	8,24	µg/h
Korrelationskoeffizient (r) =	0,9978	3-24h

Datum	Fabert (PHA)	Dr.Seiffert (PHA)

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	SPM 907	Ch.-B.:	20201028
Wirkstoff :	SPM 8224		
Sollgehalt :	15%	TDS - Fläche :	5 cm²
ABV vom :	analog OB 0469.ABV.100	Analysendatum :	

Ausgangsanalyse

Bemerkungen:
Puffer pH 6,2 KT   Freisetzungsfläche 2,55 cm²
Mäusehautdicke:1=158 µm; 2=168µm, 3=171µm, 31,4g
Alter lebend: 8 Wochen, TK-Schrank 12 Wochen SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	67,0	46,4	9,0	40,8	29,4
4	166,9	120,0	23,2	103,4	73,3
6	240,8	177,4	33,6	150,6	106,2
8	294,4	217,3	39,8	183,8	130,6
24	314,8	282,5	41,1	212,8	149,6
30	370,7	318,0	43,0	243,9	176,0
48	445,8	418,3	48,1	304,1	222,1

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=	84,4	µg
Regressionskoeffizient (m) =	6,13	µg/h
Korrelationskoeffizient (r) =	0,7917	3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	18,4	13,9	6,7	13,0	5,9
4	40,8	33,6	15,1	29,9	13,3
6	60,8	51,1	21,3	44,4	20,6
8	80,3	67,0	26,9	58,1	27,8
24	282,3	256,8	86,4	208,5	106,5
30	347,9	294,7	93,9	245,5	134,0
48	444,3	372,3	117,1	311,2	171,9

MW = Mittelwert   SD = Standardabweichung

Achsenabschnitt (b)=	-8,1	µg
Regressionskoeffizient (m) =	8,96	µg/h
Korrelationskoeffizient (r) =	0,9990	3-24h

Diffusion experiment with SPM 907 patches on full human skin

Experiment number: 907DF004

Purpose of the study:
To investigate the permeation rate of SPM 907 through skin from two newly formulated patches.

Patch:
Active Ingredient: SPM 907
Batch numbers: 20111085 and 20111087
Patch area: 5 cm²
Active ingredient content: 15% SPM 6224

Skin donor:
Birth date: 1964
Sex: female
Skin from: abdomen (belly)
Thickness of dermatomised skin: approximately 250 µm

Diffusion experiment:

Date:

Used cells:
diffusion cells with spiral groove (n=8); groove area: 0.552 cm²

Separator between acceptor phase and skin/patch:
Diachema dialysis membrane, type 10.14, supplied by Dianorm, München, Germany.
Manufactured from neutral cellulose; molar weight cut-off: 5000; thickness (dry): 25 µm.
Pretreated according to the manufacturer's recommendations.

Diameter of separator, skin and patch punch-outs: 1.8 cm

Setup diffusion cells:

Cell nr.	Cells with/without skin	Batch
1 & 2	with	20111085
3 & 4	with	20111087
5 & 6	without	20111085
7 & 8	without	20111087

Acceptor phase: PBS pH=8.2
Measured temperature waterbath: 32.0 °C
Flux of acceptor phase: 5 ml/hour
Total duration of the experiment: 72 hours, samples are collected in 3 hour periods.

Observations during dermatomisation, cell assembly, disassembly, etc.
Some of the glue from the patch disks destined for cells 7 and 8 remained on the protective foil.

Mass and volume data on the collected fractions

measured density of the used acceptor phase: 1,007 g/ml

Faktor zur Umrechnung auf cm²s: 1,812

Flux time (hours)	cell nr.	mass tubes (g) empty	mass tubes full	volume fractions (ml)	8,8284 g/ml	DryMatter µg/fraction	Fraction 1:1.812	Mittelwert	DiOH µg/ml	µg/fraction	FractionF µg/ml	Mittelwert
3	1	16,946	33,389	16,829	0,00	0,000	0,000		0,02	0,327	0,592	
	2	17,037	32,958	15,810	0,00	0,000	0,000	0,000	0,01	0,168	0,286	0,439
	3	17,103	32,828	15,715	0,00	0,000	0,000		0,02	0,314	0,570	
	4	17,146	32,969	15,703	0,00	0,000	0,000	0,000	0,02	0,314	0,569	0,569
	5	17,010	33,141	16,019	11,90	160,626	345,412		0,84	13,456	24,382	
	6	17,147	32,665	15,410	14,93	230,073	416,993	381,152	1,11	17,105	30,995	27,688
	7	17,058	32,382	15,217	19,96	303,809	550,103		1,51	22,978	41,637	
	8	17,132	32,816	15,575	22,77	354,642	642,642	596,357	1,78	27,723	50,235	45,938
6	1	16,662	33,032	16,296	0,01	0,183	0,205		0,10	1,627	2,947	
	2	16,782	32,711	16,818	0,00	0,000	0,000	0,147	0,01	0,158	0,287	1,617
	3	16,689	32,554	15,756	0,01	0,158	0,285		0,09	1,418	2,569	
	4	17,020	32,687	15,737	0,01	0,167	0,285	0,285	0,19	2,990	5,418	3,994
	5	17,187	33,320	16,021	8,16	130,780	236,683		0,60	9,613	17,419	
	6	17,128	32,667	16,433	5,93	91,518	165,830	201,356	0,67	10,340	18,736	18,077
	7	16,997	32,606	15,289	6,88	105,062	190,353		0,54	8,245	14,941	
	8	17,104	33,468	15,593	8,18	127,650	231,120	210,737	0,63	9,823	17,800	16,370
9	1	17,069	32,971	16,275	0,02	0,226	0,590		0,22	3,581	6,488	
	2	17,072	33,008	15,788	0,00	0,000	0,000	0,295	0,05	0,799	1,430	3,959
	3	17,137	32,888	15,761	0,03	0,473	0,867		0,28	4,413	7,996	
	4	17,066	33,284	15,713	0,04	0,629	1,139	0,998	0,49	7,699	13,951	10,974
	5	17,162	32,983	16,020	5,80	92,915	168,362		0,45	7,209	13,063	
	6	17,095	32,460	15,297	5,89	91,068	164,997	166,680	0,46	7,111	12,886	12,974
	7	17,048	32,447	15,297	8,32	96,677	175,178		0,50	7,648	13,859	
	8	17,093	32,769	16,245	6,04	94,205	170,699	172,939	0,43	6,707	12,152	13,006
12	1	16,841	33,300	16,245	0,05	0,812	1,472		0,49	7,960	14,424	
	2	16,877	33,256	15,769	0,01	0,158	0,286	0,879	0,15	2,366	4,286	9,355
	3	17,152	32,960	15,718	0,05	0,788	1,424		0,44	6,916	12,532	
	4	17,099	32,896	15,887	0,08	1,256	2,276	1,850	0,79	12,401	22,470	17,501
	5	17,096	33,224	16,026	7,03	112,662	204,143		0,60	9,615	17,423	
	6	16,987	32,537	15,642	4,95	76,437	138,505	171,324	0,38	5,888	10,633	14,028
	7	16,878	33,247	15,262	8,07	123,186	223,176		0,70	10,684	19,369	
	8	17,293	32,989	16,597	4,81	75,021	135,938	179,457	0,39	6,083	11,022	16,190

15	1	17,050	33,415	16,251	0.08	1,300	2,866		0.58	9,426	17,079	13,404
	2	17,230	33,182	15,791	0.04	632	1,145	1,750	0.34	5,369	9,729	
	3	17,235	33,082	15,737	0.17	2,675	4,848		1.20	18,884	34,218	31,918
	4	17,340	33,167	15,717	0.13	2,043	3,702	4,275	1.04	16,346	29,618	
	5	17,264	33,376	15,414	3.56	56,995	103,276		1.20	4,803	8,703	9,379
	6	16,879	32,401	15,278	5.02	72,446	131,273	117,274	0.30	5,649	10,055	
	7	17,091	32,476	15,278	4.15	76,896	138,973		0.36	6,570	11,904	10,897
	8	17,301	33,003	15,593	4.15	64,710	117,265	128,114	0.43	5,457	9,889	
18	1	16,756	33,089	16,219	0.12	1,946	3,827		0.69	11,191	20,279	17,414
	2	16,706	32,561	15,745	0.08	1,260	2,282	2,905	0.51	8,030	14,550	
	3	17,067	32,910	15,733	0.16	2,517	4,561		0.84	13,216	23,947	29,003
	4	16,644	32,417	15,863	0.19	2,978	5,393	4,977	1.20	18,796	34,058	
	5	17,139	33,226	15,975	3.94	62,942	114,051		0.36	4,962	8,974	9,522
	6	16,988	32,533	15,437	4.28	66,070	119,719	116,885	0.34	5,557	10,070	
	7	16,766	32,129	15,288	4.02	61,370	111,202		0.35	5,343	9,682	9,698
	8	17,198	32,872	15,566	3.65	56,812	102,944	107,073	0.35	5,292	9,589	
21	1	17,056	33,287	16,118	0.21	3,985	6,133		1.08	17,408	31,543	25,546
	2	17,178	32,924	15,637	0.13	2,033	3,583	4,908	0.69	10,789	19,550	
	3	17,124	32,659	15,626	0.22	3,438	6,229		1.02	15,938	28,860	32,949
	4	16,660	32,564	15,899	0.25	3,699	7,064	6,647	1.31	20,429	37,018	
	5	17,110	33,120	15,899	3.60	57,235	103,710		0.35	5,656	9,708	9,895
	6	17,040	32,454	15,307	3.57	54,645	99,018	101,384	0.35	5,357	9,708	
	7	17,224	32,881	15,159	3.12	47,296	85,700		0.33	5,002	9,084	9,297
	8	17,187	33,397	15,469	3.32	51,356	93,057	89,379	0.34	5,259	9,530	
24	1	17,224	32,953	16,097	0.24	3,863	7,000		1.03	16,580	30,043	28,041
	2	17,135	32,842	15,620	0.20	3,124	5,681	6,330	0.92	14,370	26,039	
	3	17,061	32,729	15,598	0.29	4,523	8,196		1.17	18,249	33,068	36,269
	4	17,198	33,163	15,659	0.31	4,823	8,740	8,468	1.40	21,783	39,470	
	5	17,100	33,514	15,874	2.90	46,034	83,414		0.28	4,446	8,054	8,603
	6	16,988	32,514	15,307	3.29	50,360	91,251	87,333	0.33	5,051	9,153	
	7	17,085	32,857	16,150	2.83	42,874	77,688		0.31	4,698	8,510	8,318
	8	16,864	33,063	16,066	2.81	43,453	78,737	78,213	0.29	4,484	8,126	
27	1	17,205	32,236	16,024	0.40	6,435	11,659		1.54	24,773	44,889	37,024
	2	16,647	32,340	16,056	0.25	3,806	7,078	9,368	1.03	16,092	29,159	
	3	17,273	32,339	15,557	0.45	7,013	12,707		1.67	26,025	47,158	43,311
	4	17,220	33,197	16,886		5,289	9,584	11,146	1.40	21,780	39,465	
	5	17,038	32,490	16,315	3.23	51,247	92,860		0.32	5,077	9,200	8,069
	6	17,177	32,434	16,151	2.54	38,900	70,488	81,873	0.25	3,829	6,938	
	7	17,056	32,818	15,455	3.13	47,422	85,929		0.35	5,303	9,609	6,025
	8				2.31	35,701	64,990	75,310	0.23	3,555	6,441	

Group	#											
30	1	17,290	33,506	16,103	0.31	4,992	9,046		1.09	17,553	31,805	32,450
	2	16,657	32,587	15,611	0.31	4,839	8,769	8,907	1.17	18,285	33,095	
	3	17,150	32,855	15,598	0.42	6,226	11,869		1.34	20,898	37,868	39,665
	4	16,463	32,138	15,666	0.40	6,550	11,282	11,576	1.47	22,882	41,462	
	5	17,135	33,110	15,864	2.94	41,881	75,888		0.25	3,966	7,186	7,611
	6	17,142	32,641	15,292	2.84	44,958	62,778	78,676	0.29	4,435	8,036	
	7	16,969	32,204	15,129	2.29	34,646	64,138		0.24	3,631	6,579	6,511
	8	17,270	32,835	16,457	2.29	35,396		63,458	0.23	3,555	6,442	
33	1	17,054	33,241	16,074	0.34	5,465	9,903		1.15	18,466	33,496	33,603
	2	17,030	32,751	15,612	0.35	5,464	9,901	9,902	1.21	18,860	34,229	
	3	17,021	32,720	15,590	0.45	7,016	12,712		1.35	21,046	38,136	39,217
	4	17,301	32,962	15,582	0.42	6,532	11,836	12,274	1.43	22,240	40,298	
	5	17,077	33,057	15,869	2.48	39,355	71,311		0.22	3,491	6,681	6,494
	6	17,112	32,537	15,318	2.75	42,124	76,328	73,820	0.24	3,676	8,238	
	7	17,088	32,346	15,154	2.80	42,431	76,885		0.30	3,093	5,604	6,921
	8	16,981	32,553	15,464	2.10	32,474	58,843	67,864	0.20	3,517	6,373	
36	1	17,190	33,348	16,105	0.28	4,509	8,171		0.84	13,528	24,513	27,817
	2	17,098	32,821	15,614	0.31	4,840	8,771	8,471	1.10	13,175	31,121	
	3	17,133	32,946	15,604	0.45	7,022	12,723		1.28	19,873	36,191	37,854
	4	17,012	32,699	15,578	0.40	6,231	11,291	12,007	1.40	21,809	38,118	
	5	17,064	33,035	15,870	2.22	35,231	63,839		0.20	3,174	5,751	6,082
	6	17,216	32,815	15,293	2.68	40,985	74,285	69,052	0.23	3,517	6,373	
	7	17,082	32,366	15,168	2.31	35,038	63,468		0.24	3,940	6,596	6,602
	8	17,107	33,310	15,469	2.38	36,816	66,710	65,069	0.24	3,712	6,727	
39	1	16,894	32,384	16,068	0.40	6,427	11,646		1.11	17,835	32,317	33,972
	2	17,161	32,598	16,605	0.41	6,398	11,593	11,619	1.26	19,662	35,628	
	3	17,071	32,854	15,884	0.51	7,948	14,401		1.32	20,571	37,274	32,856
	4	16,759	32,719	16,844	0.35	5,439	9,856	12,128	1.01	15,695	28,439	
	5	16,921	32,321	16,293	1.67	26,460	47,945		0.18	2,852	5,168	4,682
	6	16,956	32,714	15,152	1.61	24,822	44,814	46,280	0.15	2,294	4,157	
	7	16,588	32,162	15,466	1.35	29,546	53,538		0.19	2,879	5,217	5,411
	8	16,921	33,119	16,086	2.08	32,169	58,290	55,914	0.20	3,083	5,605	
42	1	17,110	32,811	15,592	0.42	6,756	12,242		1.11	17,855	32,353	33,975
	2	17,075	32,772	15,588	0.43	6,704	12,149	12,195	1.28	19,646	35,598	
	3	17,028	32,686	15,551	0.35	5,573	15,535		1.31	20,420	37,001	38,085
	4	17,059	33,046	15,876	0.49	7,620	13,808	14,671	1.39	21,616	39,168	
	5	17,077	32,484	15,300	2.06	32,546	56,973		0.18	2,858	5,178	5,361
	6	16,830	32,099	15,113	2.40	32,720	56,636	62,754	0.20	3,060	5,545	
	7	17,124	32,680	15,448	1.96	29,700	53,616		0.19	2,879	5,217	5,268
	8				1.93	29,814	54,024	53,920	0.19	2,935	5,318	

Diffusionexperiment907DF004.xls

Group	n											
45	1	17,231	33,423	16,079	0,58	9,326	16,899	16,079	1,46	23,476	42,538	42,180
	2	17,188	32,882	15,595	0,54	8,421	15,299		1,48	23,080	41,822	
	3	17,012	32,710	16,589	0,78	12,169	22,033	18,082	1,79	21,308	50,562	44,586
	4	16,846	32,508	15,553	0,50	7,777	14,091		1,37	27,904	33,610	
	5	17,043	33,189	15,049	1,64	25,992	47,098	63,250	0,25	3,984	7,218	5,763
	6	16,917	32,472	15,322	2,86	43,830	79,302		0,15	2,377	4,308	
	7	17,121	32,504	15,151	1,88	28,181	51,064	51,862	0,19	2,879	5,216	5,269
	8	17,033	33,287	15,459	1,88	29,083	52,651		0,19	2,937	5,322	
48	1	13,258	32,737	16,054	0,56	8,990	16,290	15,068	1,33	21,351	38,689	37,429
	2	17,334	32,961	15,595	0,49	7,641	13,846		1,28	19,061	36,170	
	3	16,992	32,943	15,584	0,83	9,818	17,790	16,356	1,32	20,571	37,274	37,641
	4	17,235	32,880	15,537	0,53	8,235	14,921		1,35	20,975	38,007	
	5	17,271	32,827	15,840	1,89	29,938	54,247	57,451	0,18	2,851	5,166	5,214
	6	17,118	32,491	15,285	2,19	33,474	60,655		0,21	2,904	5,252	
	7	16,971	32,677	15,114	1,99	30,077	54,500	53,567	0,19	3,774	5,751	5,535
	8	16,917	32,878	15,451	1,88	29,048	52,634		0,21	2,938	5,319	
51	1	17,206	32,633	15,798	0,62	9,794	17,748	15,258	1,49	23,537	42,848	38,257
	2	16,971	32,348	15,320	0,46	7,017	12,769		1,22	18,690	33,886	
	3	16,955	32,359	15,324	0,65	9,960	18,048	15,815	1,38	20,840	37,763	36,898
	4	16,857	32,359	15,297	0,49	7,495	13,582		1,30	19,888	36,033	
	5	16,943	32,091	15,073	1,68	25,851	46,842	50,542	0,30	4,049	7,337	7,787
	6	16,703	31,683	15,043	1,99	25,884	54,242		0,26	4,513	8,177	
	7	18,894	32,289	14,876	1,74	25,302	46,902	45,468	0,25	4,314	7,817	7,349
	8	17,029	32,929	15,189	1,60	24,302	44,035		0,25	3,797	6,880	
54	1	16,938	32,876	15,789	0,65	10,203	18,597	15,823	1,48	23,388	42,344	37,692
	2	17,242	32,368	16,323	0,47	7,202	13,049		1,22	18,234	33,040	
	3	14,706	30,071	15,327	0,71	10,862	19,716	20,089	1,38	21,151	38,325	45,019
	4	16,669	32,231	15,258	0,74	10,350	20,459		1,87	28,533	51,701	
	5	17,068	32,196	15,584	1,85	30,350	54,994	53,693	0,00	0,000	0,000	3,820
	6	17,187	32,553	15,080	1,92	28,814	52,383		0,28	4,217	7,641	
	7	17,233	32,816	14,905	1,55	23,102	41,661	42,708	0,26	3,875	7,022	6,957
	8	16,902	32,599	16,214	1,58	24,037	43,586		0,25	3,803	6,882	
57	1	17,234	32,886	15,802	0,51	8,050	14,603	13,419	1,16	18,331	33,215	32,039
	2	17,151	32,251	15,345	0,44	6,752	12,234		1,11	17,032	30,863	
	3	16,850	32,599	15,341	0,71	10,892	19,738	16,668	1,37	21,017	38,082	36,223
	4	16,890	32,590	15,294	0,49	7,494	13,738		1,24	19,964	34,364	
	5	16,504	31,674	15,591	1,99	31,026	56,219	44,761	0,37	5,769	10,463	8,093
	6	16,749	32,118	15,095	1,22	18,379	33,282		0,21	3,164	5,732	
	7		32,020	14,910	0,99	14,761	26,748	22,994	0,19	2,833	5,133	4,353
	8			15,171	0,70	10,620	19,249		0,13	1,972	3,674	

Group	n											
60	1	16,961	32,870	15,808	0.27	7,734	4,268	7,062	0.58	9,169	16,614	15,809
	2	17,106	32,547	15,385	0.23	6,391	3,527		0.54	8,281	15,005	
	3	17,156	32,622	15,369	0.32	8,906	4,915	7,820	0.57	8,755	15,884	16,393
	4	17,103	32,519	15,309	0.25	6,885	3,827		0.61	9,398	16,921	
	5	17,094	32,767	15,694	0.68	19,214	10,604	20,918	0.14	1,871	3,391	3,603
	6	17,049	32,196	15,042	0.83	22,692	12,465		0.12	2,106	3,818	
	7	16,993	32,006	14,908	0.68	18,369	10,137	18,411	0.13	1,938	3,512	3,546
	8	17,108	32,415	15,201	0.67	18,454	10,184		0.13	1,976	3,581	
63	1	17,163	33,081	15,807	0.28	6,020	4,426	7,208	0.57	8,010	16,326	15,532
	2	17,025	32,476	15,346	0.23	6,395	3,529		0.53	8,133	14,737	
	3	17,136	32,563	15,220	0.32	8,883	4,902	7,907	0.56	8,579	15,545	15,812
	4	17,104	32,511	15,300	0.25	6,931	3,825		0.58	8,874	16,080	
	5	16,849	32,534	15,578	0.68	18,628	10,280	17,868	0.12	2,107	3,818	3,602
	6	16,974	32,129	15,650	0.81	22,099	12,190		0.14	1,869	3,511	
	7	16,555	32,473	14,905	0.66	17,826	9,838	9,057	0.12	1,838	3,308	3,408
	8	17,088	32,375	15,795	0.65	17,907	9,882		0.12	1,824	3,396	
66	1	16,822	32,021	15,340	0.99	11,162	6,160	9,996	0.77	12,162	22,038	18,666
	2	17,115	32,888	16,311	0.25	6,852	3,836		0.55	8,440	14,293	
	3	17,196	32,253	15,588	0.33	9,172	5,062	39,883	1.03	8,130	28,576	21,654
	4	17,124	31,869	15,024	0.39	10,820	5,971		1.03	15,770	14,572	
	5	16,883	32,489	14,882	1.29	36,425	20,102	33,532	0.23	3,584	6,494	6,822
	6	16,919	32,835	15,606	1.57	42,740	23,587		0.23	4,056	7,350	
	7	17,174	32,527	15,331	1.23	33,168	18,305	14,404	0.24	3,572	6,472	6,405
	8	17,089	32,264	15,382	1.23	33,896	18,693		0.23	3,498	6,472	
69	1	16,857	32,663	15,300	0.55	15,752	8,693	17,091	1.04	16,438	29,785	28,921
	2	17,198	32,729	15,556	0.47	13,056	7,206		1.01	15,484	28,057	
	3	17,075	32,272	15,091	0.73	20,321	11,216	37,996	1.16	17,820	32,291	31,532
	4	17,161	32,188	14,923	0.50	13,862	7,650		1.11	16,883	30,773	
	5	17,244	32,654	15,204	1.28	35,521	19,603	34,508	0.23	3,578	6,484	6,797
	6	16,950	32,230	15,796	1.48	40,471	22,385		0.26	3,924	7,110	
	7	16,787	32,629	15,336	1.35	36,504	20,145	15,117	0.26	3,880	7,030	6,546
	8	17,198	32,621	15,338	1.18	32,508	17,940		0.22	3,345	6,061	
72	1	17,196	32,692	16,318	0.60	17,174	9,476	15,831	1.10	17,376	31,495	29,498
	2	17,192	32,273	15,691	0.47	13,000	7,208		0.99	15,182	27,510	
	3	17,092	32,188	15,075	0.66	18,340	10,122	36,653	1.00	15,336	27,798	28,605
	4	17,168	32,256	15,192	0.48	13,323	7,353		1.06	16,237	29,421	
	5	16,958			1.18	33,336	18,987	31,634	0.21	3,274	5,933	6,244
	6				1.18	37,870	20,955		0.24	3,618	6,556	
	7				1.39	31,868	17,598		0.21	3,261	5,945	5,863
	8				1.14	31,881	17,318		0.22	3,190	5,781	